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Gastroesophageal reflux disease in children: What's new right now?

Sintusek P *et al*. GERD in children

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Abstract

Gastroesophageal reflux (GER) in children is very common and refers to the involuntary passage of gastric contents into the esophagus. This is often physiological and managed conservatively. In contrast, GER disease (GERD) is a less common pathologic process causing troublesome symptoms, which may need medical management. Apart from abnormal transient relaxations of the lower esophageal sphincter, other factors that play a role in the pathogenesis of GERD include defects in esophageal mucosal defense, impaired esophageal and gastric motility and clearance, as well as anatomical defects of the lower esophageal reflux barrier such as hiatal hernia. The clinical manifestations of GERD in young children are varied and nonspecific prompting the necessity for careful diagnostic evaluation. Management should be targeted to the underlying aetiopathogenesis and to limit complications of GERD. The following review focuses on up-to-date information regarding of the pathogenesis, diagnostic evaluation and management of GERD in children.

Key Words: Gastroesophageal reflux; Gastroesophageal reflux disease; Children; Infant; Impedance study; Lower esophageal sphincter

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Core Tip: Gastroesophageal reflux disease (GERD) is a pathologic process requiring prompt assessment and treatment. The manifestations of GERD, especially in young

children vary making it a challenge to diagnose. Combined esophageal pH-MII manometry has increased the diagnostic accuracy of GERD and helped explain its pathogenesis. Medication should be targeted to the underlying GERD pathogenesis, if known, and to minimize complications.

INTRODUCTION

A combined guideline of the European and the North American Societies for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN and NAPSPGHAN respectively)[1], defined gastroesophageal reflux (GER) as the passage of gastric contents into the esophagus with or without regurgitation and vomiting and GER disease (GERD) where GER leads to troublesome symptoms that affect daily functioning and/or leads to clinical complications within the esophagus or other systems. As the clinical symptoms and signs of GERD are variable and nonspecific especially in infants and young children, it is often difficult to make a diagnosis on the basis of history or physical examination alone. Furthermore, other significant disorders that mimic GERD may need urgent attention and will need to be considered and excluded.

EPIDEMIOLOGY

The prevalence of GERD varies across studies depending on the diagnostic criteria used and the study design. A systematic review published in 2019 demonstrated that the overall pooled prevalence of GERD symptoms from 4 cross-sectional studies, was 26.9% [95% confidence interval (CI) 20.1-33.7, I2: 6.83][2] However, the prevalence of GERD in infants, across a number of prospective studies, tends to decrease with time from 25.5%[3] at age of 1 mo and 26.5%[4] at age 6 wk to 7.7%[4] at age 3 mo, 2.6%[4] and 2.9%[3] at the age of 6 mo and to only 1.1%[4] and 1.6%[5] at the age of 12 mo. An explanation of this decline is described in the pathogenesis section below. The prevalence of GERD in Asia (8.7%) is comparable to both the United States (8.9%) and Europe (8.3%-32.0%). In children, there are a number of clinical conditions that clearly predispose to the development of GERD, which include corrected esophageal atresia[6], neurological

impairment[7,8], prematurity[9-11], and cow's milk protein allergy[12-15]. In corrected esophageal atresia, for example, the prevalence of GERD diagnosed using impedance-pH monitoring and histopathology is high and up to 47.1% and 64.7%, respectively[6].

PATHOPHYSIOLOGY AND REFLUX-ASSOCIATED CONDITIONS

The main pathogenesis of GERD in children, as in adults, is abnormal transient lower esophageal sphincter relaxation (TLESR). Other factors implicated in the pathogenesis of GERD[16] include the anatomy and integrity of the antireflux barrier, as well as that of esophageal peristalsis and esophageal clearance (Table 1 and Figure 1).

Transient lower esophageal sphincter relaxation

The lower esophageal sphincter (LES) pressure tends to increase in infants with increasing gestational age[17-19]. Normally, LES relaxation follows swallowing or primary peristalsis of the esophagus. However, TLESR or a relaxation of the LES that is not preceded by swallowing can occur leading to pathologic reflux. TLESR can stimulate by increasing intraesophageal pressure as a result of crying, gastric distension and respiratory diseases. TLESR could be demonstrate in infants since gestational age of more than 28 wk[18,19]. Interestingly, many studies found that TLESR do not occur more in healthy persons comparing to patients with GERD[18,20]. Patients with GERD are more likely to have acid reflux than normal persons might explain this finding[21,22]. In addition, several protective mechanisms can contribute to the pathogenesis of GERD.

The anatomy of antireflux barrier

The antireflux barrier consists of the LES, the diaphragmatic pinchcock and angle of His (Figure 1). The LES a 1-2 cm high pressure zone located at the junction between the esophagus and the stomach and is comprised of intrinsic (lower esophageal muscle fibers) and extrinsic components (oblique sling muscle fibers from the stomach and musculofacial sling from the diaphragm). This is further supported by a short length of intra-abdominal esophagus as well as the angle of His or esophagogastric angle, the

acute angle formed between the cardia and abdominal part of LES[23]. This composite anti-reflux barrier acts in normality as a physiologic sphincter between the high stomach (intra-abdominal) pressure compared to the lower pressure in the esophagus (intra-thoracic) and thus to prevent the regurgitation of gastric contents along the pressure gradient into the esophagus.

In infants, alongside TLESRs, the underdevelopment of abdominal part of LES and angle of His are likely to explain the high prevalence of GERD in the infantile period[24,25]. Where a hiatal hernia is present in patients, the separation of the LES and the crural diaphragm acts to significantly impair the antireflux barrier and contribute to the increase in acid exposure of the esophagus and GERD.

Esophageal peristalsis and clearance

To prevent esophageal mucosal injury from the movement of gastric contents into esophagus after LES relaxation, secondary esophageal peristalsis with clearance of the refluxate back into the stomach is considered a main protective mechanism. Moreover, an upright position can further help volume clearance by gravity. Apart from mechanical clearance, the acid content of any refluxate can be neutralized by both swallowed saliva and esophageal secretions. In infants, volume clearance is less effective due to their mostly recumbent position. During sleep, the reduced frequency of primary and secondary esophageal peristalsis may contribute to precipitate GERD[1,16]. Any disorder that primarily (*e.g.*, esophageal atresia, achalasia) or secondarily (esophagitis) affects oesophageal motility may increase the predisposition to GERD[26-29]. Moreover, delayed gastric emptying or gastroparesis, often a transient phenomenon in children after infection, can cause postprandial reflux from gastric distension stimulating LES relaxation[30].

Others

Interestingly, a postprandial acid pocket phenomenon has been well described by Fletcher *et al*[31] They describe a floating "pocket" of an unbuffered reservoir of gastric

acid that may become exposed to the esophagus during LES relaxation. The role of the acid pocket in the pathogenesis of GERD has been reported but limited to adult studies[32,33].

In addition, esophageal mucosal defense may be compromised in a number of conditions such as esophagitis from eosinophilic or other inflammatory diseases as well as infections. A defect in esophageal mucosal defense can lead to esophageal dysmotility and reflux esophagitis can be superimposed. As the esophageal mucosa contains receptors sensitive to acid, temperature and volume, their destruction in severe esophagitis might explain the hyposensitivity with reflux injury in children with Barrett esophagus and corrected esophageal atresia[34]. A high index of suspicion and intensive evaluation and monitoring, including with histopathology of esophagus, are needed in such patients.

In extraesophageal manifestation of GERD, such as upper airway diseases or ENT problems, there are many proposed pathways such as GER induced vagally mediated aspiration or insufficiency of upper esophageal sphincter (UES) function[24,34-38].

CLINICAL MANIFESTATIONS

The manifestations of GERD can vary from an asymptomatic presentation or non-specific symptoms such as irritability in infants, frequent vomiting, failure to thrive, unexplained anemia, difficult to treat respiratory symptoms through to more specific ones such as heartburn in older children. However, a high index of suspicion or the presence of alarm features, may require early investigation to either exclude other mimickers or confirm the diagnosis of GERD (Table 2).

INVESTIGATION

There has been no single gold standard tool to diagnose GERD in children. In practice, therapeutic trials of medication and follow-up can be considered in older children with a typical presentation of GERD such as heartburn but these may not reliable in infants[39]. If there is no response after an 8-week trial of PPI or in the presence of alarm

features, investigations are necessary to confirm or rule out GERD. The major limitation of all diagnostic tools is that the normal values for each parameter are not well established in infants and children. A number of investigations have been used to distinguish GERD from other worrisome disorders that mimic GERD.

Ultrasound has high sensitivity and positive predictive value for GERD as it can assess both anatomy of esophagus and real-time refluxate. It is a non-invasive tool with some evidence-based studies supporting its fair sensitivity (76%-100%) and specificity (50%-100%) compared to pH studies[40-43]. A study by Charoenwat *et al* noticed the presence of a shorter abdominal esophageal length, increased cervical and abdominal esophageal wall thickness, diameter and angle of His in Thai children diagnosed with GERD (n = 22, median age of 1.6 years) compared with healthy children (n = 23), however, these differences failed to reach statistical significance[44] (Figure 3). Moreover, the reliability of the test depends on the individual experience of the radiologist[45].

Barium (contrast) swallow and upper gastrointestinal studies (meal ± follow through) are used to evaluate anatomical abnormalities of esophagus, stomach and proximal small bowel such as tracheoesophageal fistula, achalasia, hiatus hernia, midgut malrotation ± intermittent volvulus. Furthermore, the barium study can roughly evaluate the transit time of esophagus and stomach but lacks standardized protocols and normal values. Although, episodes of reflux are commonly observed during these procedures, there is poor correlation with an abnormal reflux index from 24-h pH study[46]. Overall, such contrast studies are neither sensitive nor specific tests for GER or GERD and should not be used for diagnosis.

Endoscopy is generally utilized where esophagitis is suspected in patients with significant clinical issues such as recurrent vomiting, unexplained anemia, hematemesis, positive stool occult blood or high-risk groups (corrected esophageal atresia, eosinophilic esophagitis, immunocompromised hosts that are prone to have esophageal infection). Eosinophilic esophagitis and eosinophilic gastrointestinal disease can present with symptoms and signs similar to that of GERD and its diagnosis requires histopathology of esophageal tissue (Figure 4). Clinician should be aware that severe

esophagitis in GERD rarely present with pain[34] and there is a poor correlation between the severity of symptoms and esophagitis. In children with extraesophageal symptoms such as cough and wheezing, up to one third had microscopic esophagitis[47], suggesting endoscopy may also have a role in children with extraesophageal symptoms.

pH-monitoring, combined MII-pH monitoring test and combined Video-MII-pH monitoring test

The pH-monitoring test has largely been replaced with MII-pH monitoring that can provide more data not only of acid reflux but also of other types (weakly acid, nonacid, liquid or air) as well as the proximal extent of reflux (Figure 5). However, pH-monitoring does retain value especially with regards to wireless pH recording, that minimizes disruption of patients during monitoring and allows for prolonged assessment of up to 5 d[48,49]. Similar with other diagnostic tools for GERD in children, there remains a lack of normal values hence the results of the test should be interpreted with caution. The most recent combined ESPGHAN- NAPSPGHAN guidelines recommend using the MII-pH study to correlate persistent troublesome symptoms with reflux episodes[1]. Recently, researchers have reported enhancements of the technique such as the use of combined VDO-MII-pH studies (Figure 6) in high-risk children with corrected esophageal atresia. Many children with corrected esophageal atresia may develop reflux esophagitis without specific symptoms or signs, however, Maholarnkij *et al*[6] found the trend of specific symptom association with the refluxate by using real-time Video recording and MII-pH monitoring. In this study, vomiting, irritability or unexplained crying and cough were the most common symptoms associated with reflux during combined Video-MII-pH monitoring. Hence, this novel tool might help the clinicians to diagnose GERD by increasing the symptom association index from MII-pH monitoring.

Oropharyngeal pH monitoring

UES dysfunction is thought to represent a major factor underlying the pathogenesis of the extraesophageal symptoms of GERD. Oropharyngeal pH monitoring should, in theory, detect abnormal acid reflux in this area and thus the cause of such symptoms. However, studies to date report conflicting results regarding the correlation of oropharyngeal pH monitoring and full-column refluxes detected by pH-impedance monitoring[50-56]. These studies were limited by small numbers of participants as well as equipment available to measure the pH above the LES and at the UES in children. The linkage of acid reflux from below the LES to that above the UES may have been impacted by the longer frequency used to detect acid in the proximally implanted Dx-pH probe (every 0.50 s) compared to the distal MII-pH recording (every 0.02 s)[52]. There is no connection between oropharyngeal pH events and pH-impedance events, according to a systematic review in adults[53]. Moreover, there were no significant differences in oropharyngeal acid exposure between PPI responder, partial responders and nonresponders in adult patients with laryngeal symptoms[54].

Esophageal manometry and esophageal manometry with pH-MII monitoring

Esophageal manometry can help clarify the role of esophageal dysmotility leading to ineffective esophageal clearance in the pathophysiology of reflux however is an invasive test relies on cooperation from children undergoing the studies[57-59].

In a study by van Lennep *et al*[60], even though esophageal manometry with or without 24-h pH impedance study was successfully tested in children (> 90%),complete interpretation is limited in children under the age of 4.

Esophageal manometry with pH-MII monitoring has a potential role in the assessment of extraesophageal symptoms such as aspiration pneumonia from esophageal stasis[1], or to improve the cough-reflux correlation[61].

Electrogastrography (EGG) is a noninvasive test to study the electrophysiology of stomach, and in turn assess for the presence of gastroparesis or gastric hypomotility as potential pathogenic factors for GERD[59,62]. Studies suggests significantly higher pooled prevalence of EGG abnormalities in GERD patients comparing to healthy adults[63] and

children[64]. However, the protocol and techniques for EGG study are quite variable between centers.

Due to the limitations of current investigative procedures used to diagnose extraesohageal manifestation of GERD, biomarkers have been proposed for use in diagnosing this type of GERD. Studies have suggested using of pepsin, lipid-laden macrophages and, bilirubin[65-71]. However, their diagnostic efficacy has not been established, and most call for invasive procedures like bronchoscopy to get the necessary samples, which restricts their application.

Therapeutic trial: PPI or transpyloric feeding

Studies to support the role of diagnostic trials of PPI and transpyloric feeding in children are scarce[72,73]. Trials of transpyloric feeding to confirm GERD are not specific given improvements in symptoms of vomiting or feeding intolerance may also be seen in mimickers of GERD such as severe gastroparesis[74].

Treatment

In GER, nonpharmacological treatment and close follow-up are enough often sufficient while in GERD more therapeutic options are usually needed with careful consideration of treatments that balance optimal symptom resolution with predictable side effects.

Nonpharmacological treatment

Nonpharmacological treatments are recommended in infants suspected GER that include the following.

Head and body position after meals: So far there is no recommendation for prone, right lateral position in infants as it may increase the risk of sudden infant death syndrome[34]. One study has demonstrated the effectiveness of supine 40 degree anti-Trendelenburg position using "Multicare-AR Bed" in decreasing symptoms and acid reflux by using MII-pH monitoring[75]. However, a retrospective study demonstrated more reflux episodes in the upright position compared to supine position in children

and infants, probably as a result of frequent TLES while they were awake[76]. However, nocturnal reflux has been associated with prolonged esophageal acid exposure due to decreasing esophageal clearance from gravity, this may support the rational of upright head position after feeding in infants.

Extensively hydrolysed protein or amino acid formulas are considered in infants suspected of GERD. The nonspecific signs and symptoms provide a challenge for the diagnosis of cow's milk protein allergy. The Cow Milk Symptom Score (CoMiSS) might be used to evaluate infants before and after treatment of cow's milk protein allergy (CMPA), but it is not considered as a diagnostic tool[77]. If there is no clinical improvement after 4-8 wk trial, CMPA is unlikely. Recently CoMiSS was modified in which a score of more than 10 (previously more than 12) in infants supported a diagnosis of CMPA[78]. Moreover, the stool pattern was changed from the Bristol Stool Scale to the Brussels Infant and Toddlers Stool Scale instead as a better user-friendly tool for non-toilet trained children. The updated CoMiss score is shown in Table 3.

Thickened formula use is associated with a significant decrease of visual regurgitation but not of acid reflux monitored by MII-pH[34]. Hence, thickening products have been recommended for use in infants with GER[1]. However, there has been a rising concern about the safety of thickeners; for example the inorganic arsenic in rice cereal[1], risk of necrotizing enterocolitis from xanthum gum and carob bean[79,80]. Moreover, rice cereal can be digested by amylase in breast milk limiting its use with breast milk.

Pharmacological treatment (Table 4)

If infants and children's symptoms are not resolved with nonpharmacological treatment, medication can be considered. The most common medications include drugs that promote esophageal and gastric motility, tighten the LES, and acid suppressants to reduce esophageal mucosal injury. Acid suppressant agents: proton pump inhibitor (PPI)[81,82] and H_2-receptor antagonist (H_2RA)[83] are used as the gold standard of GERD treatment[1]. PPIs are more effective than H_2RA for acid suppression[84] and there is no

tachyphylaxis with prolonged used. However, they may not be effective in non-acid or weakly acid reflux and the prolong used can cause side effects especially increased rates of respiratory and gastrointestinal infection[85-88]. In addition, some of H_2RA were withdrawn from the market because of the increasing risk of malignancy from nitrosamine contamination[89]. It should also be noted that acid suppression has potential effects on the integrity of gut microbiota[90] with worsening the symptoms, although the concomitant use of probiotics have been suggested to mitigate this issue[91-93].

Prokinetic agents: The effectiveness of prokinetic agents was evidenced in adult population but much less so in children. Common prokinetics used in infants and children include domperidone[94], metoclopramide[95] and erythromycin. Domperidone and metoclopramide act as $5HT_4$ agonists in the stomach and gut while erythromycin stimulate motilin receptors in the antral area of stomach[96]. These medications are therefore believed to be useful in children and infants who have GERD owing to gastroparesis and to speed up upper GI transit time. Limitations for the use of domperidone and metoclopramide include significant potential side effects of QT prolongation[97] and extrapyramidal symptoms[98], respectively. When administered for a long time, erythromycin can potentially cause tachyphylaxis[99]. There is little available information on other prokinetic drugs such as mosapride, itopride, prucalopride and renzapride in children. Another prokinetic agent with direct effects on the LES is baclofen. Baclofen is a gamma-aminobutyric acid (GABA)-B receptor agonist and appear to act by reducing transient relaxations of LES. Baclofen has also been shown to accelerate gastric emptying[100-103]. However, the adverse effects of dyspepsia, drowsiness and dizziness[104] can limit its use in infants and children.

Alginate antacids: Since the late 1990s, compound alginate preparations were changed to become aluminum-free and safe for infants. As Cochrane review in 2014 indicated moderate evidence of this agent for the improvement of reflux in infants in short term follow-up[105-108]. Alginate antacid act by creating a barrier and appear

effective for rapid symptom resolution regardless of the stimulus (acid, pepsin, bile, or mixed)[109]. Evidence for their use in GERD is limited[110].

Esophageal mucosal protection: Sucralfate is the well-known mucosal protective drugs that is composed of sucrose sulfate and aluminum hydroxide. It acts by inhibiting peptic digestion, providing mucosal protection and stimulating tissue growth and healing[111]. Recently, the novel medical device, Esoxx™, was developed and mainly composed of two mucopolysaccharides, mixed to a mucoadhesive gelling agent and a viscosity regulator compound to form a mucoadhesive formulation. It adheres to the esophageal mucosa and act as barrier against refluxed gastric content[112-115]. However, Esoxx™ was originally developed for use in adults[114,116], and there is a rising concern about applying it in children[117]. A recent publication has demonstrated the efficacy and safety of Esoxx™ in adolescents[118] but the data in younger children is scarce.

Probiotics: Because of the safety profiles of probiotics, this agent has been used worldwide in infants and children for many purposes such as acute diarrhea, colic, and regurgitation. A large RCT study in 589 term infants demonstrated the significant efficacy of Lactobacillus reuteri DSM 17938 to prevent colic. In the same RCT, the author also demonstrated the efficacy of this probiotic in decreasing the mean number of regurgitations per day[119]. Hence, probiotics are prescribed widely in clinical practice to prevent or treat GER. However, in GERD, there has been no strong evidence for their use and further research is warranted.

Surgery and therapeutic endoscopic management

Transpyloric feeding is often considered in GERD that might be subside with time for example; in severe gastroparesis from medications such as opioids, preterm infants[72,73] or from critical illness such as children in intensive care units[120]. There is, however, increasing data supporting its use as a viable alternative therapeutic strategy to surgery even for high-risk patients, such as those with neurological impairment, given their similar overall efficacy and rates of complications[121,122]. For transpyloric feeding recurrent tube dislodgement provides one of most common complications.

In the highest risk patients especially those with severe neurodisability and life-threatening complications of GERD, surgical or laparoscopic fundoplication has traditionally been considered the therapy of choice[123-126].

However, there are the need for re-fundoplication and concurrent medication use in the most difficult to treat patients[34]. In addition, transoral incisionless fundoplication (TIF) procedure have been increasing performed in patients with severe GERD[127-130]. Even though the recurrence rate in long term follow-up in children with severe neurological impairment was high, the complications from TIF were minimal[131]. As a result, some selective cases with GERD might benefit from this low-risk procedure.

CONCLUSION

The recognition, diagnosis and treatment of GERD, especially in young children remains challenging. It requires to be differentiated from GER as well as GERD mimics, which is best approached using careful clinical assessment, especially in high risk groups, paying attention to alarm features and the selective use of investigations, where necessary. There remains, however a lack of a gold standard tool for GERD. Management should aim to target underlying aetiopathology and minimize complications. These may be managed through a variety of non-pharmacological and pharmacological strategies with surgery limited to very selected indications. Further studies to optimize the diagnosis and management of GERD are still needed. Table 5 summarize the update diagnostic investigation and treatment for children with suspected GERD and figure 7 proposed the step of diagnosis and management children with suspected GERD

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